Counterterrorism-related Specific Immune Globulins: Problems and Challenges in Development

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Counterterrorism and Specific Immune Globulins

- Vaccinia immune globulin (VIG): for treatment of life-threatening complications of smallpox vaccine
- Botulism immune globulin (BIG): for treatment of botulism poisoning
- Anthrax immune globulin (AIG): for treatment of subjects not responsive to antibiotics (proposed)
- Other IG's against other agents are/may be considered (proof-of-concept in animal studies)

Challenges (1)

- Product
  - Donor selection/vaccination protocols
    - Live vaccines - ? Viremia
    - Co-vaccination with live vaccines (if enrolled in vaccine programs)
    - Viral validation in manufacturing
  - Potency
    - Bioassays or binding assays?
    - Standards for testing
    - Lot release
    - Dosing

Challenges (2)

- Clinical
  - Efficacy testing: often product cannot be tested in “real life” scenario, e.g. vaccinia immune globulin for progressive vaccinia
  - Role of the animal rule
  - Limitations animal testing (BSL-4 agents)

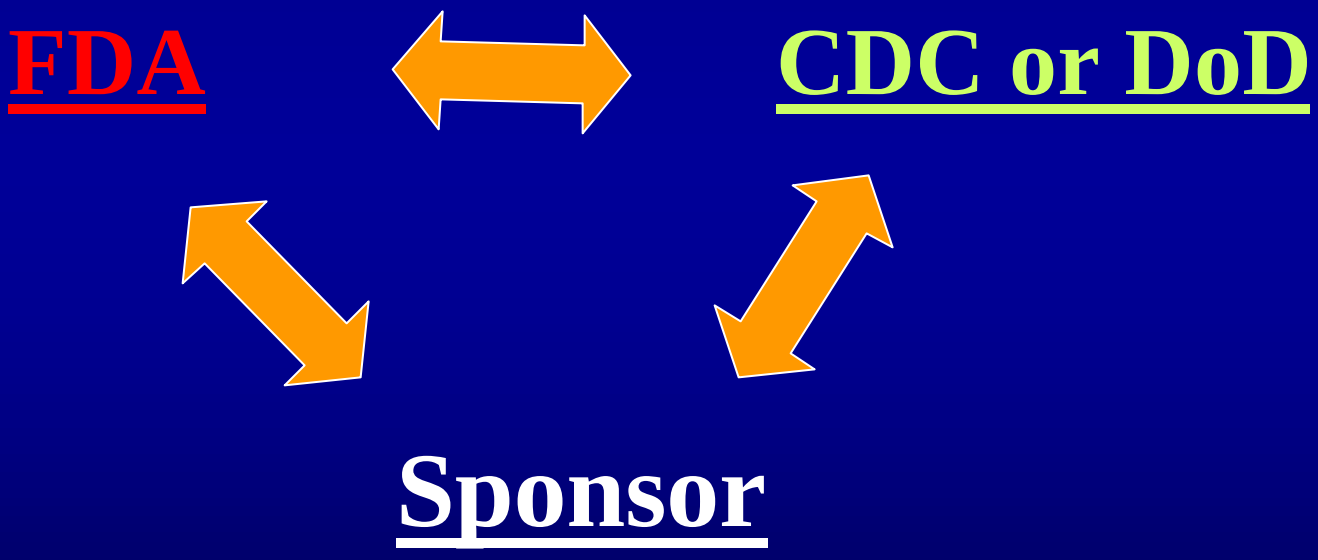
Challenges (3)

- Provision of material in IND stage
  - IND's for indications (often CDC; industry, other government)
  - E-IND's (unexpected events; case-by-case)
- Provision of material long-term (as long as the need exists)
  - Stability monitoring
  - Maintaining supply of product over years; determining when additional lots will be needed

Challenges (4)

- Timing
  - Production timelines (GMP's, and scaleup)
  - Licensure: possible eligibility for Fast Track procedures
    - Priority review
    - Rolling review

Coordination/Problem Solving Early



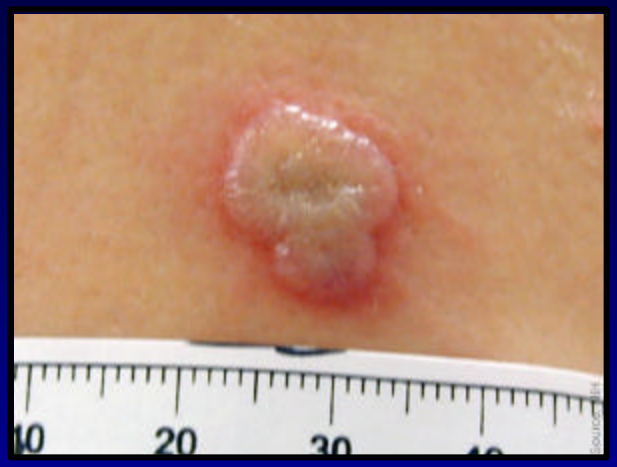
Vaccinia Immune Globulin: Case Study in Development

- Vaccinia immune globulin, intravenous, human
  - Historically licensed product; very low demand until post 9-11
  - Diminishing potency of old supplies
  - Manufacture of new material indicated

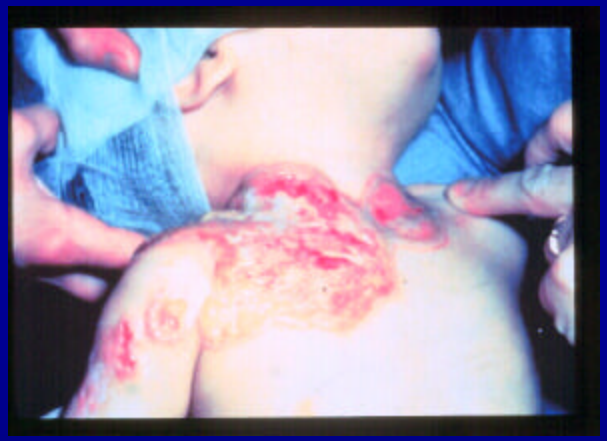
Historical Uses of VIG Products: Complications of Smallpox Vaccination

- **Eczema vaccinatum***
- **Progressive vaccinia (vaccinia necrosum; gangrenosum)***
- **Ocular vaccinia*** (but NOT keratitis)
- Generalized vaccinia* (+/-)
- Prophylaxis against eczema vaccinatum

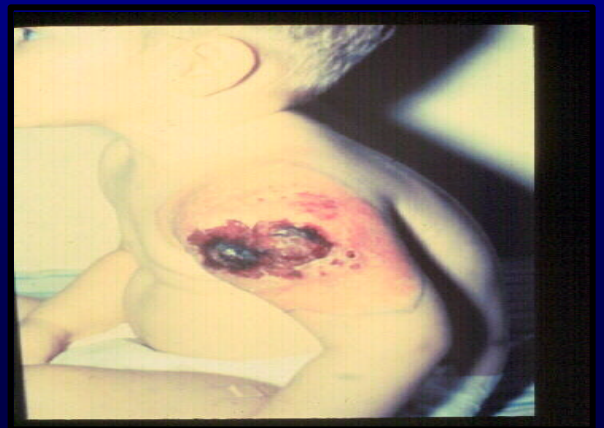
Smallpox Vaccination Complications – Mortality Without VIG Treatment



Normal Vaccination — **0%**



Eczema Vaccinatum — **30-40%**



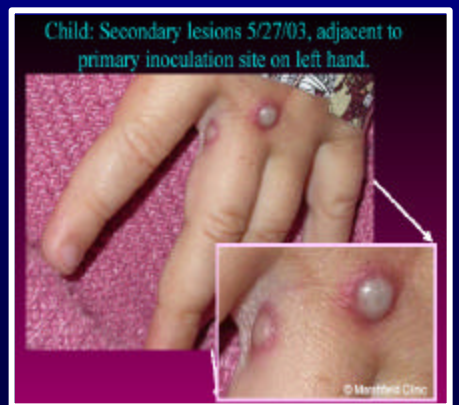
Progressive Vaccinia — **100%**

Vaccinia Immune Globulin Products

- **All are under IND**
- **All manufactured from Source Plasma of revaccinated donors**
- **Source Plasma collected 10- approx. 30 days post-vaccination**
- **New VIG's manufactured using S/D treatment and nanofiltration steps for viral clearance**

Challenges in Development and Use of VIGIV

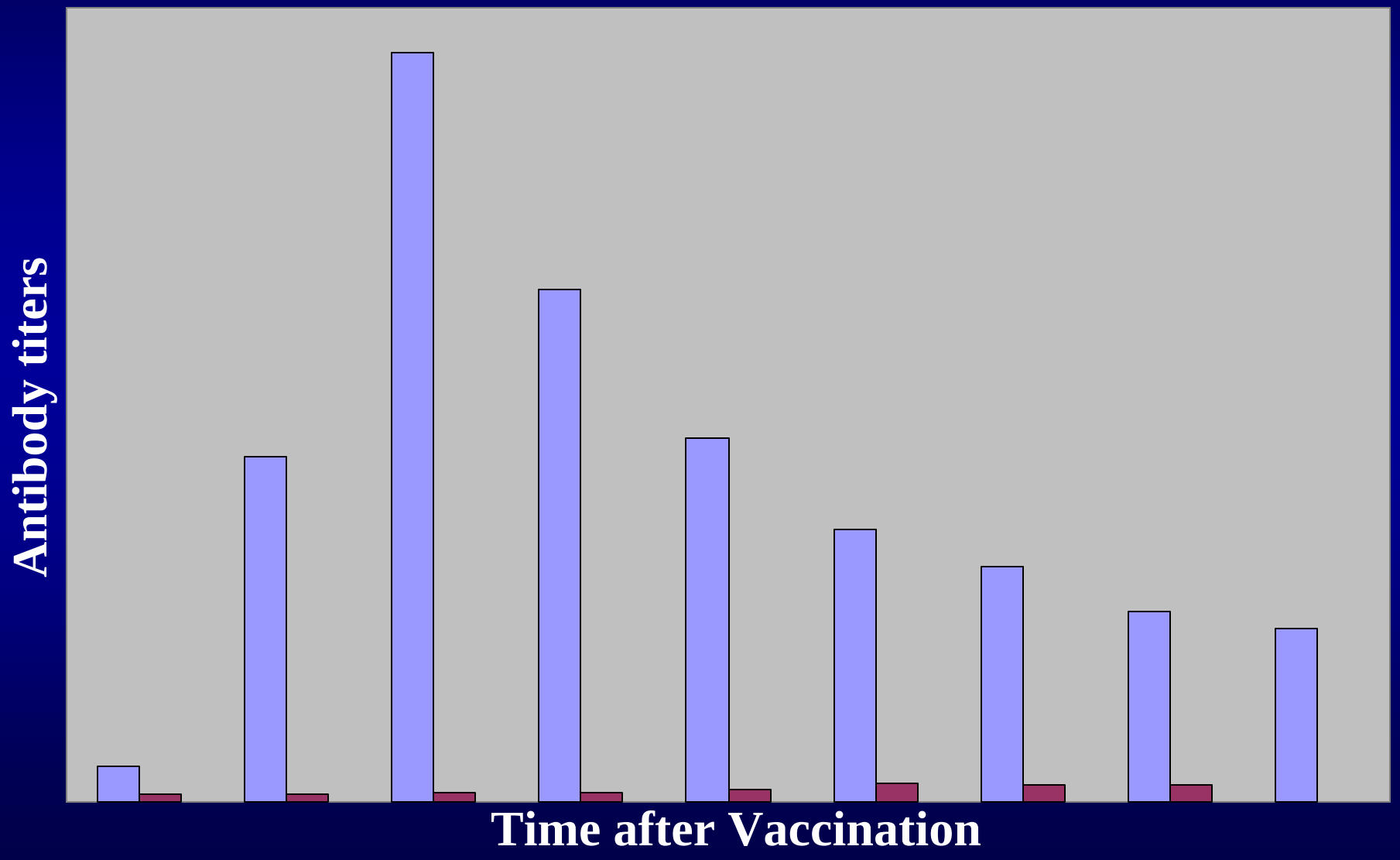
- Plasma donors and live vaccination (vaccinia)
- Potency testing for VIG (lot release)
- Clinical study: real treatment studies not possible in pre-event scenario
- Addressing post-exposure prophylaxis
- Emerging possible indications (the unexpected)
  - Myopericarditis?
  - Monkeypox prophylaxis or treatment?



Smallpox Vaccination and Donor Deferral

- Published January 19, 2003
- Deferral for vaccinees:
  - 21 days after vaccination, OR
  - Until scab falls off
  - WHICHEVER IS LONGER
- Rationale
  - Possibility of viremia
  - Consequences of viral transmission to recipient could be severe

DONOR RESPONSE TO DRYVAX VACCINE



Plasma Collection for VIG Products

- VIG products historically made from plasma collected early post-vaccination
- In vitro studies (B-gal assay; plaque assays): no plaques observed with VIG alone; no evidence live virus in products
- Need to maximize collection of high-titer material

Evidence-based decision-making

- Historical information about viremia
- Publications on capacity of plasma derivative processing steps to clear vaccinia
- CBER and Industry research on the question of viremia in smallpox vaccinees
- Maximizing product safety

Vaccinia Viremia (?)

- **Herzberg, Kremmer, 1930[1]**
  - **8/17 normal children post vaccine**
  - **titered by bioassay in rabbits**
  - **strains various (cattle lymph)**
  - **viremia days 3-15; mainly day 6-7**

- **Also reported 1953 (journal not available)**

[1]Zentralblatt fur Bakteriologie 1930; 115:271-80

Vaccinia Viremia (?)

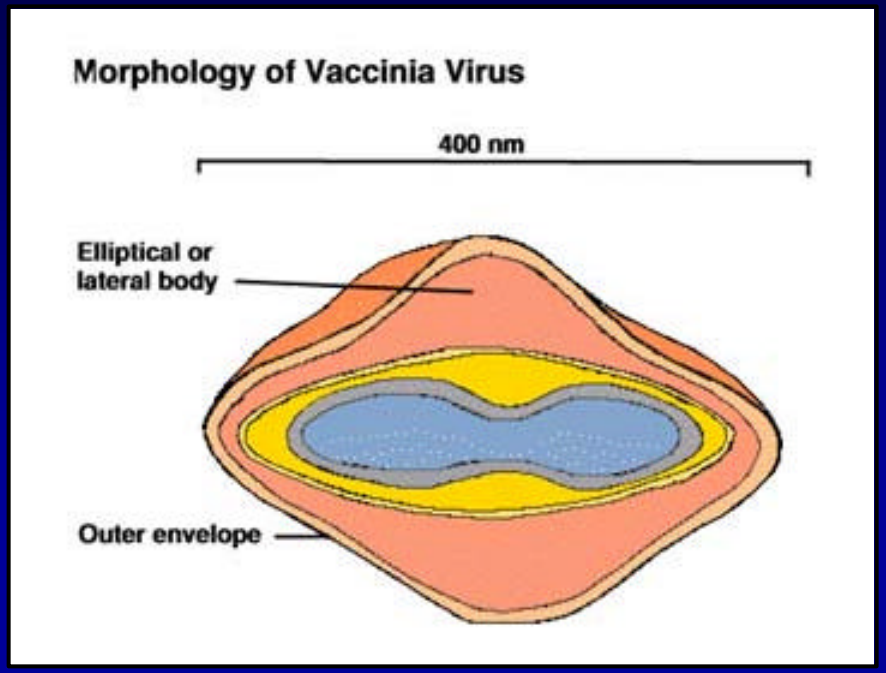
- **Not seen in “over 100” patients studied (no data shown)[1]**

FDA and Industry: plaque assays for Vaccinia in blood from recently vaccinated people

[1] **Kempe, CH, Pediatrics 1960; 26:176-89**

Vaccinia Virus Clearance Potential of VIGIV Manufacturing Processes

Vaccinia Virus



- **Enveloped**
- **DNA**
- **400 nM size**

Vaccinia Virus and S/D Treatment of FVIII *

	Logs Inactivation					
Virus	Minutes S/D (TNBP 0.3% / Triton X-100 1.0%)					
	0.25	1	10	30	60	120
Vaccinia	1.0	2.5	3.8	4.4	4.7	4.7
HSV-1	>5.1	>5.1	Nd	Nd	Nd	Nd
Sindbis	4.9	5.4	>5.6	Nd	Nd	Nd

*Resistance of Vaccinia Virus to Inactivation by S/D treatment of Blood products. Roberts, P. Biologicals 2000; 28: 29-32

Vaccinia Virus and S/D Treatment of Fraction II Precipitate (0.3% TNBP/1% PS80, 60-180 min.)*

		Recovered		Eliminated	
Virus	Added	Pre-S/D	After S/D	Clearance	Reduction
Vaccinia	7.75	6.88	4.41	3.34	2.47
HIV-1	> 11.5	> 11.5	<1.5	>10	>10
VSV	7.43	7.32	<1.86	>5.57	>5.46

* Inactivation and elimination of viruses during preparation of human intravenous immunoglobulin. Uemura et al, Vox Sang 1994; 67:246-54.

Plasma Fractionation – Viral Clearance Steps for VIGIV

All recently manufactured new IND products have 2 viral inactivation steps that are expected to clear vaccinia:

1. Solvent-detergent treatment

1. Nanofiltration

Vaccinia Viral Validation for VIGIV Products

- **Donor exclusion for 21+ days post-vaccination would result in loss of high-titer plasma**
- **Working Assumption: Viremia likely to be low level, rare and/or intermittent, if present at all, in normal vaccinated donors**
- **Testing for post-vaccination viremia ongoing in several laboratories (no positive reports to date, but studies are not finished, and not prospectively designed for viremia monitoring)**
- **Viral clearance studies suggest vaccinia can be inactivated by S/D treatment, but that vaccinia is relatively resistant compared to other enveloped viruses**
- **Nanofiltration is expected to remove vaccinia due to its large size**

- **Process-specific validation will provide enhanced assurance of safety**

Potency of VIG

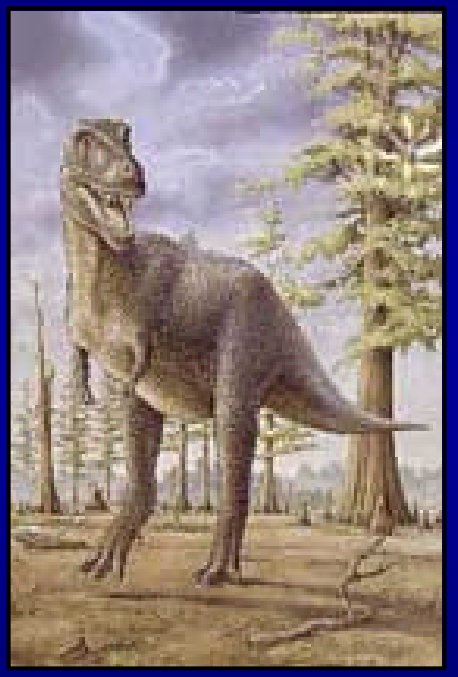
- Bioassays vs. solid-phase (e.g. ELISA) for lot release

  POTENCY does not always equal BINDING

  because non-neutralizing (e.g. non-useful) antibodies may bind to antigens on a plate
- CBER has stated preference for bioassay use for VIG products (neutralization)
- CBER in-house assays developed for VIG potency
  - Research-level
  - To enable product characterization
  - To increase bioassay understanding and capabilities

The Old Method: Plaque Reduction Neutralization Test (PRNT)

- First developed in 1960's
- Slow (3-6 days)
- Requires large amounts of plasma
- Day-to-day and person-to-person variability
- Time-consuming (manual counting of plaques); not automated
- Difficult to consistently reproduce
- Difficult to transfer to new labs



CBER RESEARCH: Meeting the Needs
H. Golding et al, OVRR, CBER, FDA

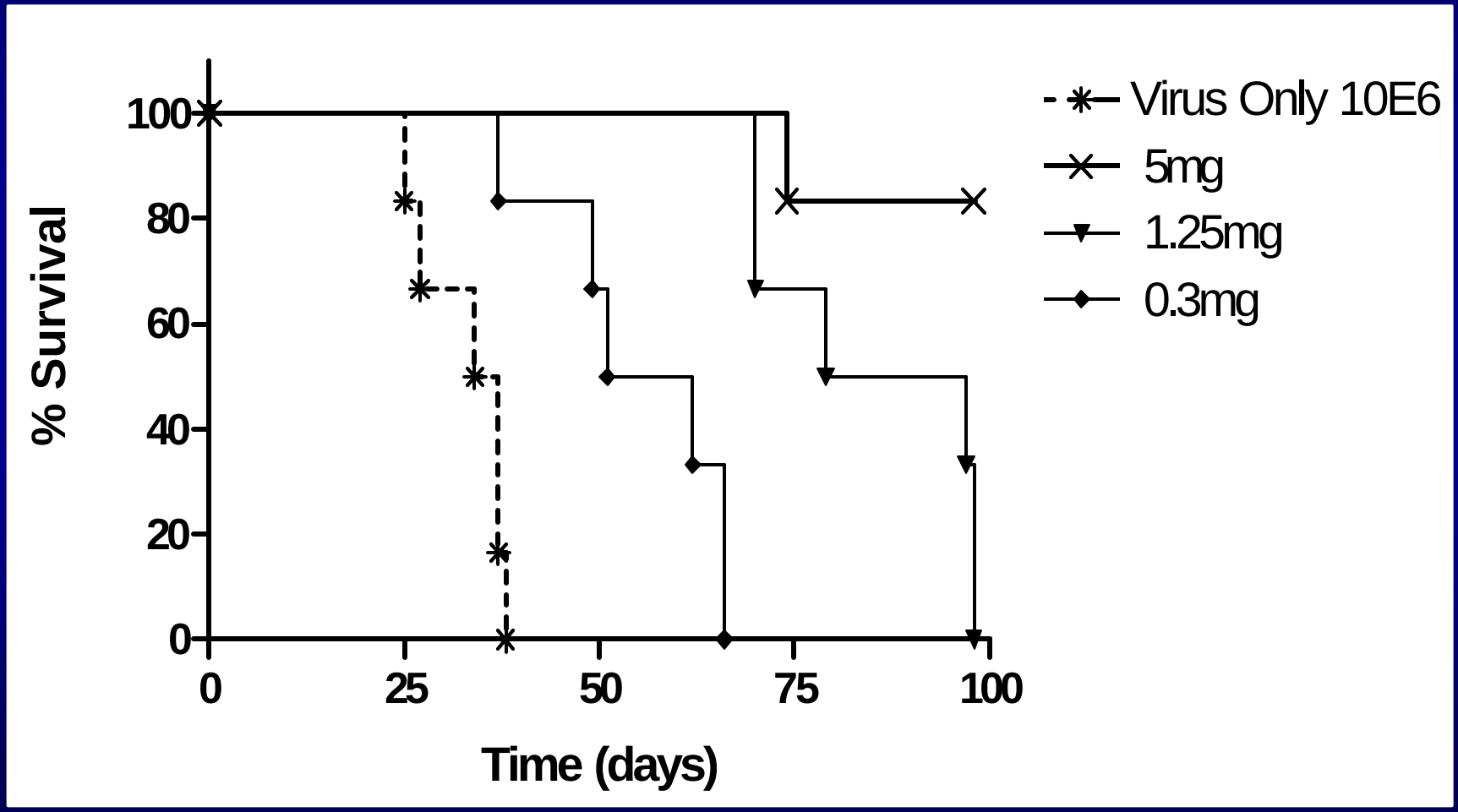
- We developed an improved test using a beta-galactosidase reporter-gene containing virus:
  - Faster (24 hr); High throughput; important for large scale evaluation of many samples in clinical trials
  - Read-out: automated; Machine reads color-change
  - Sensitive, quantitative, reproducible
  - Easy to transfer to manufacturers/DOD

In vivo assays

- CBER developed an in vivo model of potency in severely immunocompromised (SCID) mice

- May reflect neutralization of forms of virus not easily cultured, e.g. extracellular enveloped form,
- Useful for comparison to in vitro bioassays
- Provides useful early assurance of likelihood of efficacy
- Other animal models also under development

CBER Research: Protective Effect of VIGIV at Different Doses in SCID Mice



CBER/Manufacturer Testing and Provision of Interim VIG Standard

- MPHBL* VIGIV, manufactured under GMP conditions
- Aliquotted, frozen; no loss of potency with 2 freeze-thaws
- Tested in 3 different laboratories for plaque neutralizing activity, with good agreement
- Available from CBER (scottd@cber.fda.gov)

* Massachusetts Biologic Laboratories

Clinical Studies for Licensure of CT Products: VIGIV Strategy

- How to perform clinical studies pre-event?
  - Actual studies for the disease states (EV and PG) not possible due to very low rate of these complications. Licensure based upon PK equivalence and safety data. PK not inferior ($\geq$ 0.8) to VIG given I.m.
  - Studies in animal models (e.g. tailpox, SCID mice)
  - Discuss with CBER for product-specific advice
- Post-approval commitments; use of Animal Rule

Current Thinking: Clinical Trials for Licensure of VIGIV, Indications

- (2002) New product indications limited to treatment of VIG-treatable vaccinia vaccine complications; labeling specific to data provided by manufacturer of each product
- (2003) Potential consideration post-exposure prophylaxis possibilities
  - Immunocompromised vaccinees
  - Exfoliative skin conditions
  - Note indication in previously licensed product (Baxter): post-exposure prophylaxis for exfoliative/inflammatory skin conditions, including eczema [not based on controlled studies].

Unexpected Events during IND Phase

- Requests for use of product for post-exposure prophylaxis

- Unanticipated clinical scenarios

Clinical Issues: Recent Use of VIG

- To date, no cases of progressive vaccinia (PG), or confirmed eczema vaccinatum (EV)
  - 0/ 454,856 military vaccinees[1]
  - 0/ 37,478 civilian vaccinees[2]
- VIG requested for[3]:
  - Prophylaxis EV in recently vaccinated burn patient (1)
  - Ocular vaccinia (1)
  - Post-vaccination discovery of pregnancy

[1] Col. J. Grabenstein, Military Vaccines Agency, USAMC, presented to the Advisory Committee for Immunization Practices (ACIP) 6/18/03

[2] G. Mootrey, National Immunization Program, ACIP 6/18/03

[3] Discussed at ACIP 6/18/03

Use of VIG(IV) in Pregnancy

- Estimates of fetal vaccinia risk extremely low[1]
  - NYC 1942: 0/ 170,000 pregnant vaccinees
  - U.S. 1967-7: 1/ 5,600 to 17,000 primary vaccinations
- Inadvertent vaccinations in most cases due to very early (undetectable) pregnancy, or to post-vaccination conception
- CDC advice " Women should contact their healthcare provider regarding use of VIG. Currently, CDC's ACIP does not recommend preventive use of VIG for pregnant women."[2]
- CDC has established a pregnancy registry for follow-up of vaccinated pregnant women

[1] S. Goldstein, CDC National Immunization Program

[2] (www.bt.cdc.gov/agent/smallpox/vaccination/preg-factsheet.asp)

Smallpox Vaccination and Myo/pericarditis

- Newly recognized complication in U.S.
- DOD: 46 cases/ 454, 856 vaccinees
- Civilian: 22/ 37,000 vaccinees
- No fatalities
- Etiology - possibly immune-mediated;
  VIG use would have to be carefully weighed
- Ongoing follow-up of cases for long-term sequelae

Monkeypox and VIG Use

- VIG use, if any, was discussed
- Note that CDC has recommended smallpox vaccination for people who were likely to have been exposed to monkeypox (http://www.cdc.gov/ncidod/monkeypox/smallpoxvaccine_mpox.htm)
  - Contraindicated for certain immunocompromised people

CT Product Development: Common Themes

- Uniqueness of some products
- Need to support supply and supply capability closely in the interests of public health
- Stability of products that may be “on the shelf” for prolonged time – monitoring critical to maintain supply of product
- Evolving recommendations as assays, testing, and product characterization continue
- Frequent discussions among FDA, sponsors, and manufacturers are important !